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# Use of a Suspoemulsion to Improve Bioavailability of a DCS Class IV Compound

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SUMMARY

Enabling formulations are used by the pharmaceutical industry to help improve bioavailability of compounds with low solubility and permeability properties. Suspoemulsions are a combination strategy of using permeation enhancers in a lipid phase, with drug molecules incorporated as a solid nanosuspension in the aqueous phase to maximise oral exposure. Here, a suspoemulsion is created by bead milling a classical drug suspension to reach nano size range and combining with a lipid blend of Labrasol ALF and Capmul MCM. This formulation increased oral bioavailability from 5% to 24%. The exact mechanism of this improvement is hypothesised but would need further work to establish.



## INTRODUCTION

Compounds classed as DCS (Developability Classification System) Class IV are challenging to dose due to poor solubility, and permeability (Rosenberger *et al*, 2018). Typically, these compounds have low oral bioavailability; making it challenging to achieve the required exposure in preclinical toxicology studies. Here a DCS Class IV compound, with an oral bioavailability of 5% in mice when dosed in DMSO:PEG400:PBS (15:40:45), was reformulated using a suspoemulsion to improve exposure.

Suspoemulsions have historically been used by the agrochemical industry to dual dose two Active Ingredients with different properties (Mulqueen, 2003). Here it has been used to combine two enabling formulation strategies to increase both permeability and solubility of a DCS Class IV compound. Permeability through the addition of high concentrations of permeation enhancers via emulsification and solubility by increasing the dissolution rate using a nanosuspension.

## MATERIALS AND METHODS

Following materials were used in this study Labrasol ALF (Gattefosse, UK), Capmul MCM (Barentz, UK), Lecithin, PEG 200, DMSO and Sodium Caprate (Sigma Aldrich , UK).

Dispersant screening studies were performed by suspending the compound in a range of dispersant solutions and assessing the resulting suspensions for aggregation via polarised light microscopy.

Nanosuspensions were prepared by bead milling standard suspensions with 0.5 mm Zirconium-Silica beads on a roller mixer for 48 hours. Resulting suspensions were characterised for dissolution behaviour in FaSSIF using Apparatus II dissolution (Agilent 708-DS) with fibre optic UV detection (Agilent Cary 60), and particle size by Dynamic Light Scattering (Malvern Zetasizer Ultra).

The suspoemulsion was prepared by adding an oil-emulsifier blend, with the compound predissolved, to

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the pre-prepared nano-suspensions and left to stir until a homogenous suspoemulsion was formed.

*In-vivo* studies was performed at CRL Edinburgh and approved by the Animal Welfare and Ethical Review Body. Formulations were dosed at 6 mg/kg (oral gavage) or 1 mg/kg (IV in DMSO:PEG 200:PBS (10:40:50)) to female CD1 mice.

## RESULTS AND DISCUSSION

Following the dispersant screening, lecithin at 1% w/v was selected as an appropriate dispersant. This resulted in a nanosuspension with a mean particle size of 412 nm that was stable for more than one week. Also, a 40-fold increase in dissolved drug, when compared to a standard suspension (Figure 1), was observed. Therefore, it was considered that a stable nanosuspension, which potentially addressed the solubility challenges, was formed.

To improve intestinal permeability the addition of penetration enhancers, Labrasol ALF and sodium caprate, was assessed. It was possible to add up to a 10% w/v of Labrasol ALF and 2% w/v sodium caprate to the nanosuspension without negatively affecting both particle size (207 and 439 nm respectively) and dissolution performance (Figure 1).

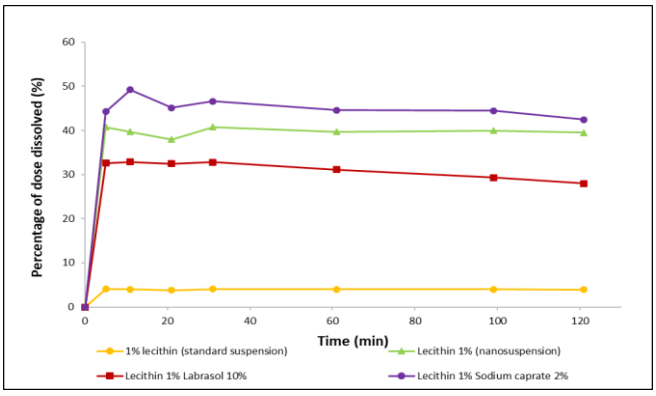


***Fig. 1.*** *Dissolution of nano-suspensions for development.*

To increase the concentration of penetration enhancers, the addition of an emulsion phase, using Capmul MCM, to the suspension was evaluated (i.e., a suspoemulsion). This increased the Labrasol ALF concentration to 37.5% w/v, however no increase was observed with sodium caprate. The addition of Capmul MCM increased the dissolved fraction of the compound in the final formulation. Four formulations were progressed into a PK study (Figure 2).

Following the PK Study (Figure 2) a 1.2-fold increase in bioavailability was observed with the nanosuspension when compared to the original study (i.e., 6% compared to 5%). The addition of penetration enhancers had mixed results; no increase seen with Labrasol, but a 1.5-fold increase observed with sodium caprate compared to the nanosuspension (i.e., 9% compared to 6%). However, a 4-fold increase in bioavailability was observed with suspoemulsion compared to the nanosuspension (i.e., 24% compared to 6%), representing a significant improvement.

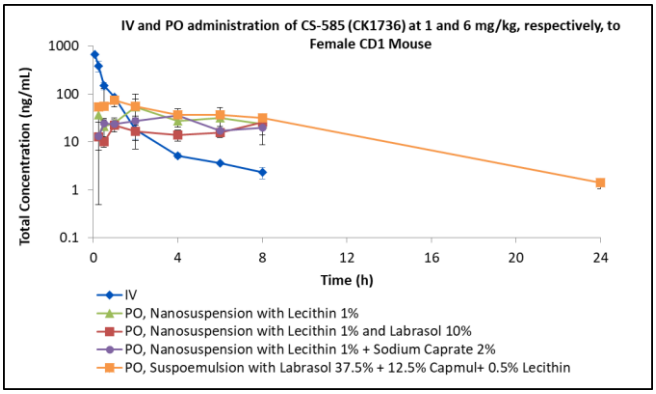


***Fig. 2.*** *Plasma concentration of API over 24 hours.*

This result is hypothesised to be due to an interplay of the below mechanisms, which require further work to fully elucidated.

1) Increased dissolution rate due to the nanosuspension.

2) High levels of penetration enhancers improving permeability.

3) The lipid component improving *in-vivo* solubility and stabilising the supersaturated state after the rapid dissolution.

## CONCLUSIONS

A suspoemulsion increased the oral bioavailability of a DSC Class IV compound from 5% to 24%. This represents an alternative approach for difficult to dose compounds in a preclinical setting.

## REFERENCES

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